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Procter & Gamble

The Procter & Gamble Company
Ivorydale Technical Center
5299 Spring Grove Avenue, Cincinnati, Ohio 45217-1087

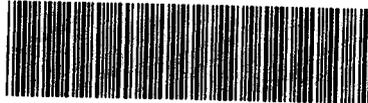
March 3, 1998

8EHQ - 0398 - 14133

Document Processing Center (TS-790)
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U.S. Environmental Protection Agency
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RE: TSCA Section 8(e) Submission



8EHQ-98-14133

1-naphthol (CAS# 90-15-3)

ATTN: TSCA Section 8(e) Coordinator

This submission is made in accordance with TSCA Section 8(e) requirements and discharges any TSCA Section 8(e) responsibilities that exist for The Procter & Gamble Company regarding the information described herein. We do not believe the data described in this submission reasonably support the conclusion that the subject material presents a substantial risk of injury to human health or the environment.

This submission provides results from an Oral (Gavage) Developmental Toxicity Study of 1-naphthol in rats. While the study final report is not yet available, interim data summarized by the lab in the attached tables included observations of neurotoxicity in female rats treated with 400 mg/kg of 1-naphthol consistent with those identified by the Agency as reportable under TSCA Section 8(e). These clinical observations included, but were not limited to, the following: decreased motor activity, ataxia, lost or impaired righting reflex, twitches, body jerks, lacrimation, dilated pupils and salivation. These signs apparently increased in frequency as the treatment period progressed up to termination of the dosing regimen (dosing period = gestation days 7-17). These behavioral observations decreased to control levels (essential none) after the dosing phase of the study stopped. Necropsy data did not show any test article related findings. A copy of the study protocol is attached following the data tables.

P&G does not currently manufacture, import, distribute, or process the subject material for any TSCA regulated purpose. We have handled and will continue to handle this material with appropriate caution in keeping with our standard practice for handling all chemical substances.

If you wish further information, please contact me at (513) 627-6145.

Very truly yours,

THE PROCTER AND GAMBLE COMPANY

W. E. Bishop, Ph.D.
Manager
Risk, Policy & Regulatory Sciences

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Attachments



88980000102



Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044

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Date Sent: 16-FEB-98

Pages including this
cover page: 10

Comments:

Attached are final summary tables for your Oral (Gavage) Developmental Toxicity Study of RE-1141.02 in Rats (Argus Study 916-020; P&G Study HBE BTS 0704/02). Please remember that these are unaudited data and are being provided for informational purposes only.

Adverse clinical observations for the 400 mg/kg/day dosage group included decreased motor activity, ataxia, lost of righting reflex, impaired righting reflex, lethargy, disorientation, twitches, body jerks, lacrimation, chromorhinorrhea, dilated pupils, perinasal substance, excess salivation, and perioral substance. Chromorhinorrhea, dilated pupils and lacrimation were also noted in a few 100 mg/kg/day dosage group rats and chromorhinorrhea was noted once in a 20 mg/kg/day dosage group rat. All other clinical observations were not dosage-dependent and are common in laboratory studies with this species.

Body weight gains and body weights were reduced for the 400 mg/kg/day dosage group throughout treatment, compared to the control group. The 20 and 100 mg/kg/day dosage groups were comparable to the control group.

Absolute and relative feed consumption values were also reduced for the 400 mg/kg/day dosage group during treatment, compared to the control group. The feed

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consumption values of the 20 and 100 mg/kg/day dosage groups were generally comparable to the control group.

Caesarean-sectioning data was based on 23 (92%), 25 (100%), 25 (100%) and 25 (100%) pregnant rats on the 0 (Vehicle), 20, 100 and 400 mg/kg/day dosage groups, respectively. All Caesarean-sectioning and litter data were comparable across treatment groups and within the historical control of the Testing Facility.

Totals of 339, 348, 372 and 379 fetuses were examined externally for fetal alterations in the 0 (Vehicle), 20, 100 and 400 mg/kg/day dosage groups, respectively. There were no gross external findings.

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ARGUS RESEARCH LABORATORIES, INC.

PROTOCOL 916020

ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RB-1141.02 IN RATS

TABLE (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY

TABLE RANGE: *****021698

| DOSAGE GROUP | MAXIMUM POSSIBLE INCIDENCE | | | |
|-------------------------------|----------------------------|---------|---------|---------|
| | I | II | III | IV |
| APPEARS NORMAL | 350/ 25 | 350/ 25 | 351/ 25 | 350/ 25 |
| APPEARS NORMAL | 322/ 25 | 344/ 25 | 334/ 25 | 279/ 25 |
| DEAD | 25 | 25 | 25 | 25 |
| SCHEDULED SACRIFICE | 0/ 0 | 0/ 0 | 1/ 1 | 0/ 0 |
| MASS - LESION | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| LESION | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| DEPRESSION | 0/ 0 | 0/ 0 | 0/ 0 | 129/ 23 |
| DECREASED MOTOR ACTIVITY | 0/ 0 | 0/ 0 | 0/ 0 | 69/ 22 |
| ATAXIA | 0/ 0 | 0/ 0 | 0/ 0 | 47/ 15 |
| LOST RIGHTING REFLEX | 0/ 0 | 0/ 0 | 0/ 0 | 69/ 21 |
| IMPAIRED RIGHTING REFLEX | 0/ 0 | 0/ 0 | 0/ 0 | 48/ 14 |
| LETHARGY | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| EXCITATION | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| TWITCHES | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| BODY JERKS | 0/ 0 | 0/ 0 | 0/ 0 | 10/ 6 |
| EYES - NOSE | 0/ 0 | 0/ 0 | 0/ 0 | 7/ 5 |
| LACRIMATION | 0/ 0 | 0/ 0 | 1/ 1 | 57/ 17 |
| ENOPHTHALMOS | 13/ 1 | 0/ 0 | 0/ 0 | 0/ 0 |
| CHROMORRHINORRHEA | 0/ 0 | 1/ 1 | 5/ 3 | 7/ 6 |
| DILATED PUPIL | 0/ 0 | 0/ 0 | 5/ 5 | 108/ 24 |
| PERINASAL SUBSTANCE | 0/ 0 | 0/ 0 | 0/ 0 | 3/ 3 |
| CHROMODACRYORRHEA | 0/ 0 | 0/ 0 | 2/ 1 | 0/ 0 |
| MISCELLANEOUS | 0/ 0 | 1/ 1 | 0/ 0 | 0/ 0 |
| INCISOR(S) GROWN IN | 1/ 1 | 0/ 0 | 1/ 1 | 1/ 1 |
| ALOPECIA NO LONGER APPARENT | 0/ 0 | 0/ 0 | 2/ 1 | 0/ 0 |
| SWOLLEN SNOUT | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| ORAL-BUCCAL | 0/ 0 | 0/ 0 | 0/ 0 | 160/ 25 |
| EXCESS SALIVATION | 0/ 0 | 5/ 1 | 0/ 0 | 0/ 0 |
| INCISORS: MISSING/BROKEN | 0/ 0 | 0/ 0 | 1/ 1 | 17/ 10 |
| PERIORAL SUBSTANCE | 0/ 0 | 0/ 0 | 2/ 1 | 0/ 0 |
| INCISORS: MISALIGNED | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| RRSPIRATION | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| RALES | 0/ 0 | 0/ 0 | 0/ 0 | 17/ 7 |
| SKIN - FUR | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| LOCALIZED ALOPECIA: BACK | 0/ 0 | 0/ 0 | 0/ 0 | 7/ 1 |
| LOCALIZED ALOPECIA: UNDERSIDE | 16/ 2 | 0/ 0 | 1/ 1 | 0/ 0 |
| URINE-STAINED ABDOMINAL FUR | 0/ 0 | 0/ 0 | 0/ 0 | 45/ 9 |
| LOCALIZED ALOPECIA: LIMBS | 8/ 1 | 0/ 0 | 13/ 2 | 11/ 1 |

MAXIMUM POSSIBLE INCIDENCE = (DAYS x ANIMALS)/NUMBER OF ANIMALS EXAMINED PER GROUP

ARGUS RESEARCH LABORATORIES, INC.
 PROTOCOL 916020 : ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RE-1141.02 IN RATS

TABLE (PAGE 1): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY

| DOSAGE GROUP | MATERNAL BODY WEIGHT (G) | | | |
|--------------|--------------------------|--------------------|----------------------|---------------------|
| | I 0 MG/KG/DAY | II 20 MG/KG/DAY | III 100 MG/KG/DAY | IV 400 MG/KG/DAY |
| RATS TESTED | N | 25 | 25 | 25 |
| PRGNANT | N(%) | 25(100.0) | 25(100.0) | 25(100.0) |
| DAY 0 | MEAN±S.D. | 244.9 ± 11.7 | 244.9 ± 11.8 | 245.5 ± 11.7 |
| DAY 7 | MEAN±S.D. | 285.0 ± 15.6 | 284.2 ± 13.7 | 283.0 ± 13.4 |
| DAY 8 | MEAN±S.D. | 289.3 ± 17.4 | 290.2 ± 14.3 | 285.2 ± 11.6 |
| DAY 9 | MEAN±S.D. | 294.6 ± 16.8 | 295.3 ± 15.5 | 290.4 ± 13.6 |
| DAY 10 | MEAN±S.D. | 301.7 ± 16.7 | 302.2 ± 15.8 | 297.7 ± 14.0 |
| DAY 11 | MEAN±S.D. | 309.4 ± 19.8 | 309.3 ± 15.4 | 304.5 ± 15.3 |
| DAY 12 | MEAN±S.D. | 316.4 ± 21.2 | 316.0 ± 16.7 | 312.1 ± 15.2 |
| DAY 13 | MEAN±S.D. | 321.8 ± 19.6 | 321.4 ± 16.7 | 307.1 ± 19.3 |
| DAY 14 | MEAN±S.D. | 329.1 ± 21.0 | 326.4 ± 17.2 | 318.0 ± 15.5 |
| DAY 15 | MEAN±S.D. | 339.9 ± 22.3 | 337.3 ± 18.8 | 325.6 ± 16.1 |
| DAY 16 | MEAN±S.D. | 353.1 ± 22.8 | 349.9 ± 19.4 | 337.7 ± 15.7 |
| DAY 17 | MEAN±S.D. | 366.5 ± 23.6 | 363.6 ± 19.5 | 349.0 ± 16.2 |
| DAY 18 | MEAN±S.D. | 387.7 ± 25.5 | 382.2 ± 21.7 | 369.2 ± 17.6 |
| DAY 19 | MEAN±S.D. | 401.6 ± 26.4 | 396.1 ± 20.7 | 383.7 ± 21.4 |
| DAY 20 | MEAN±S.D. | 425.9 ± 28.5 | 420.6 ± 24.6 | 395.6 ± 23.4 |
| | | | | 403.9 ± 27.1 |

This table restricted to pregnant animals.
 DAY = DAY OF GESTATION

ARGUS RESEARCH LABORATORIES, INC.
 PROTOCOL 916020 : ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RE-1141.02 IN RATS

TABLE (PAGE 1): MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY

| DOSAGE GROUP DOSAGE | DAYS | | | |
|------------------------------------|---------------|---------------|---------------|---------------|
| | 0 MG/KG/DAY | 20 MG/KG/DAY | 100 MG/KG/DAY | 400 MG/KG/DAY |
| RATS TESTED | N | | | |
| | 25 | 25 | 25 | 25 |
| PREGNANT | N(%) | | | |
| | 23 (92.0) | 25 (100.0) | 25 (100.0) | 25 (100.0) |
| MATERNAL BODY WEIGHT CHANGE (G) | MEAN±S.D. | | | |
| | 0 MG/KG/DAY | 20 MG/KG/DAY | 100 MG/KG/DAY | 400 MG/KG/DAY |
| DAYS 0 - 7 | +40.2 ± 11.3 | +39.4 ± 7.8 | +37.5 ± 9.6 | +38.2 ± 10.2 |
| DAYS 7 - 8 | +4.2 ± 7.8 | +5.9 ± 6.0 | +2.2 ± 7.3 | -1.3 ± 6.6 |
| DAYS 8 - 9 | +5.3 ± 7.3 | +5.1 ± 5.3 | +5.2 ± 5.2 | +2.5 ± 5.0 |
| DAYS 9 - 10 | +7.1 ± 6.5 | +6.9 ± 5.2 | +7.3 ± 5.1 | +6.5 ± 5.5 |
| DAYS 7 - 10 | +16.6 ± 5.0 | +17.9 ± 7.5 | +14.7 ± 8.6 | +7.8 ± 5.8 |
| DAYS 10 - 13 | +22.1 ± 6.2 | +19.2 ± 6.1 | +20.4 ± 7.5 | +16.1 ± 5.7 |
| DAYS 13 - 15 | +16.0 ± 6.6 | +16.0 ± 5.6 | +19.6 ± 4.2 | +18.0 ± 4.8 |
| DAYS 15 - 18 | +47.9 ± 7.8 | +44.9 ± 9.8 | +46.0 ± 9.0 | +34.4 ± 7.8 |
| DAYS 7 - 18 | +102.7 ± 14.4 | +98.0 ± 15.5 | +100.8 ± 16.7 | +76.3 ± 12.2 |
| DAYS 18 - 20 | +38.1 ± 7.0 | +38.3 ± 7.5 | +35.8 ± 9.4 | +44.4 ± 6.3 |
| DAYS 7 - 20 | +140.8 ± 17.4 | +136.3 ± 17.6 | +136.5 ± 19.4 | +120.7 ± 15.6 |
| DAYS 0 - 20 | +181.0 ± 21.8 | +175.7 ± 18.2 | +174.0 ± 22.2 | +158.9 ± 21.4 |

This table restricted to pregnant animals.
 DAYS = DAYS OF GESTATION

ARGUS RESEARCH LABORATORIES, INC.
 : ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RE-1141.02 IN RATS
 PROTOCOL 916020

TABLE (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - GESTATION - SUMMARY

| DOSAGE GROUP | I | | | | II | | | | III | | | | IV | | | |
|-----------------------------------|-------------|--|--|--|--------------|--|--|--|---------------|--|--|--|---------------|--|--|--|
| | 0 MG/KG/DAY | | | | 20 MG/KG/DAY | | | | 100 MG/KG/DAY | | | | 400 MG/KG/DAY | | | |
| DOSAGE | 25 | | | | 25 | | | | 25 | | | | 25 | | | |
| RATS TESTED | 25 | | | | 25 | | | | 25 | | | | 25 | | | |
| PREGNANT | 23 (92.0) | | | | 25 (100.0) | | | | 25 (100.0) | | | | 25 (100.0) | | | |
| MATERNAL FEED CONSUMPTION (G/DAY) | | | | | | | | | | | | | | | | |
| DAYS 0 - 7 | MEAN±S.D. | | | | 23.5 ± 2.5 | | | | 23.6 ± 1.9 | | | | 23.0 ± 2.6 | | | |
| DAYS 7 - 10 | MEAN±S.D. | | | | 25.0 ± 2.4 | | | | 24.9 ± 2.2 | | | | 23.8 ± 2.8 | | | |
| DAYS 10 - 12 | MEAN±S.D. | | | | 26.8 ± 3.7 | | | | 26.8 ± 2.4 | | | | 26.6 ± 3.4 | | | |
| DAYS 12 - 15 | MEAN±S.D. | | | | 27.8 ± 2.8 | | | | 26.7 ± 3.1 | | | | 27.9 ± 2.7 | | | |
| DAYS 7 - 15 | MEAN±S.D. | | | | 26.5 ± 2.2 | | | | 26.0 ± 2.1 | | | | 26.1 ± 2.3 | | | |
| DAYS 15 - 18 | MEAN±S.D. | | | | 32.4 ± 2.5 | | | | 32.0 ± 2.5 | | | | 31.8 ± 3.0 | | | |
| DAYS 7 - 18 | MEAN±S.D. | | | | 28.1 ± 2.2 | | | | 27.6 ± 2.1 | | | | 27.6 ± 2.3 | | | |
| DAYS 18 - 20 | MEAN±S.D. | | | | 30.6 ± 2.5 | | | | 30.5 ± 2.5 | | | | 29.5 ± 4.2 | | | |
| DAYS 7 - 20 | MEAN±S.D. | | | | 28.5 ± 2.2 | | | | 28.0 ± 2.1 | | | | 27.9 ± 2.4 | | | |
| DAYS 0 - 20 | MEAN±S.D. | | | | 26.8 ± 2.1 | | | | 26.5 ± 1.8 | | | | 26.2 ± 2.1 | | | |
| DAYS 7 - 20 | MEAN±S.D. | | | | 26.8 ± 2.1 | | | | 26.5 ± 1.8 | | | | 26.2 ± 2.1 | | | |
| DAYS 7 - 25 | MEAN±S.D. | | | | 26.8 ± 2.1 | | | | 26.5 ± 1.8 | | | | 26.2 ± 2.1 | | | |
| DAYS 10 - 25 | MEAN±S.D. | | | | 26.8 ± 2.1 | | | | 26.5 ± 1.8 | | | | 26.2 ± 2.1 | | | |
| DAYS 15 - 25 | MEAN±S.D. | | | | 26.8 ± 2.1 | | | | 26.5 ± 1.8 | | | | 26.2 ± 2.1 | | | |
| DAYS 20 - 25 | MEAN±S.D. | | | | 26.8 ± 2.1 | | | | 26.5 ± 1.8 | | | | 26.2 ± 2.1 | | | |
| DAYS 25 - 25 | MEAN±S.D. | | | | 26.8 ± 2.1 | | | | 26.5 ± 1.8 | | | | 26.2 ± 2.1 | | | |

This table restricted to pregnant animals.

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

ARGUS RESEARCH LABORATORIES, INC.
 : ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RE-1141.02 IN RATS
 PROTOCOL 916020

TABLE (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - GESTATION - SUMMARY

| DOSAGE GROUP DOSAGE | MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - GESTATION - SUMMARY | | | |
|--------------------------------------|--|--------------------|----------------------|---------------------|
| | I 0 MG/KG/DAY | II 20 MG/KG/DAY | III 100 MG/KG/DAY | IV 400 MG/KG/DAY |
| RATS TESTED | N | 25 | 25 | 25 |
| PREGNANT | N (%) | 25 (100.0) | 25 (100.0) | 25 (100.0) |
| MATERNAL FEED CONSUMPTION (G/KG/DAY) | | | | |
| DAYS 0 - 7 | MEAN±S.D. | 88.8 ± 8.3 | 89.2 ± 6.9 | 87.3 ± 9.1 |
| DAYS 7 - 10 | MEAN±S.D. | 85.4 ± 5.2 | 85.1 ± 7.5 | 82.4 ± 9.2 |
| DAYS 10 - 12 | MEAN±S.D. | 86.6 ± 8.9 | 86.7 ± 6.8 | 87.3 ± 10.1 |
| DAYS 12 - 15 | MEAN±S.D. | 85.0 ± 7.0 | 82.1 ± 9.0 | 86.3 ± 7.4 |
| DAYS 15 - 18 | MEAN±S.D. | 89.7 ± 4.4 | 89.3 ± 6.9 | 88.8 ± 7.0 |
| DAYS 7 - 18 | MEAN±S.D. | 86.6 ± 3.3 | 85.6 ± 6.3 | 86.1 ± 6.0 |
| DAYS 18 - 20 | MEAN±S.D. | 75.6 ± 4.0 | 76.4 ± 6.5 | 73.5 ± 8.9 |
| DAYS 7 - 20 | MEAN±S.D. | 84.5 ± 3.1 | 83.7 ± 6.0 | 83.7 ± 5.8 |
| DAYS 0 - 20 | MEAN±S.D. | 80.8 ± 3.3 | 80.5 ± 5.0 | 80.1 ± 4.7 |

This table restricted to pregnant animals.
 DAYS = DAYS OF GESTATION
 [] = NUMBER OF VALUES AVERAGED

ARGUS RESEARCH LABORATORIES, INC.

PROTOCOL 916020 : ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RH-1141.02 IN RATS

TABLE (PAGE 1): CABSAREAN-SECTIONING OBSERVATIONS - SUMMARY

| DOSAGE GROUP | I | | II | | III | | IV | |
|---|-------------|------------|--------------|------------|---------------|------------|---------------|------------|
| | 0 MG/KG/DAY | | 20 MG/KG/DAY | | 100 MG/KG/DAY | | 400 MG/KG/DAY | |
| RATS TESTED | N | 25 | N | 25 | N | 25 | N | 25 |
| PREGNANT | N (%) | 23 (92.0) | N (%) | 25 (100.0) | N (%) | 25 (100.0) | N (%) | 25 (100.0) |
| DIED | N (%) | 0 | N (%) | 0 | N (%) | 0 | N (%) | 0 |
| ABORTED AND SACRIFICED | N (%) | 0 | N (%) | 0 | N (%) | 0 | N (%) | 0 |
| DELIVERED | N (%) | 0 | N (%) | 0 | N (%) | 0 | N (%) | 0 |
| ANIMALS PREGNANT AND CABSAREAN-SECTIONED ON DAY 20 OF GESTATION | N | 23 | N | 25 | N | 25 | N | 25 |
| CORPORA LUTEA | MEAN±S.D. | 16.5 ± 2.7 | MEAN±S.D. | 16.4 ± 2.9 | MEAN±S.D. | 16.6 ± 2.0 | MEAN±S.D. | 17.4 ± 2.1 |
| IMPLANTATIONS | MEAN±S.D. | 15.3 ± 2.3 | MEAN±S.D. | 14.8 ± 3.0 | MEAN±S.D. | 15.8 ± 1.7 | MEAN±S.D. | 15.8 ± 2.1 |
| LITTER SIZES | MEAN±S.D. | 14.7 ± 2.3 | MEAN±S.D. | 13.9 ± 2.9 | MEAN±S.D. | 14.9 ± 1.8 | MEAN±S.D. | 15.2 ± 2.3 |
| LIVE FETUSES | N | 339 | N | 348 | N | 372 | N | 379 |
| | MEAN±S.D. | 14.7 ± 2.3 | MEAN±S.D. | 13.9 ± 2.9 | MEAN±S.D. | 14.9 ± 1.8 | MEAN±S.D. | 15.2 ± 2.3 |
| DEAD FETUSES | N | 0 | N | 0 | N | 0 | N | 0 |
| | MEAN±S.D. | 0.0 ± 0.0 | MEAN±S.D. | 0.0 ± 0.0 | MEAN±S.D. | 0.0 ± 0.0 | MEAN±S.D. | 0.0 ± 0.0 |
| RESORPTIONS | MEAN±S.D. | 0.5 ± 0.6 | MEAN±S.D. | 0.9 ± 1.1 | MEAN±S.D. | 0.9 ± 1.2 | MEAN±S.D. | 0.6 ± 0.9 |
| EARLY RESORPTIONS | N | 12 | N | 23 | N | 22 | N | 13 |
| | MEAN±S.D. | 0.5 ± 0.6 | MEAN±S.D. | 0.9 ± 1.1 | MEAN±S.D. | 0.9 ± 1.2 | MEAN±S.D. | 0.5 ± 0.9 |
| LATE RESORPTIONS | N | 0 | N | 0 | N | 0 | N | 2 |
| | MEAN±S.D. | 0.0 ± 0.0 | MEAN±S.D. | 0.0 ± 0.0 | MEAN±S.D. | 0.0 ± 0.0 | MEAN±S.D. | 0.1 ± 0.3 |
| DAMS WITH ANY RESORPTIONS | N (%) | 11 (47.8) | N (%) | 13 (52.0) | N (%) | 13 (52.0) | N (%) | 10 (40.0) |
| DAMS WITH ALL CONCEPTUSES DEAD OR RESORBED | N (%) | 0 | N (%) | 0 | N (%) | 0 | N (%) | 0 |
| DAMS WITH VIABLE FETUSES | N (%) | 23 (100.0) | N (%) | 25 (100.0) | N (%) | 25 (100.0) | N (%) | 25 (100.0) |

ARGUS RESEARCH LABORATORIES, INC.
 ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RE-1141.02 IN RATS

TABLE (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

| DOSAGE GROUP DOSAGE | I | | | |
|--|-------------|--------------|---------------|---------------|
| | 0 MG/KG/DAY | 20 MG/KG/DAY | 100 MG/KG/DAY | 400 MG/KG/DAY |
| LITTERS WITH ONE OR MORE LIVE FETUSES | | | | |
| | N | N | N | N |
| | 23 | 25 | 25 | 25 |
| IMPLANTATIONS | | | | |
| | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. |
| | 15.3 ± 2.3 | 14.8 ± 3.0 | 15.8 ± 1.7 | 15.8 ± 2.1 |
| LIVE FETUSES | | | | |
| | N | N | N | N |
| | 339 | 348 | 372 | 379 |
| | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. |
| | 14.7 ± 2.3 | 13.9 ± 2.9 | 14.9 ± 1.8 | 15.2 ± 2.3 |
| LIVE MALE FETUSES | | | | |
| | N | N | N | N |
| | 175 | 153 | 178 | 181 |
| ‡ LIVE MALE FETUSES/LITTER | | | | |
| | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. |
| | 51.6 ± 17.9 | 43.5 ± 13.8 | 48.6 ± 12.4 | 47.9 ± 10.9 |
| LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER | | | | |
| | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. |
| | 3.64 ± 0.19 | 3.71 ± 0.22 | 3.61 ± 0.25 | 3.49 ± 0.22 |
| MALE FETUSES | | | | |
| | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. |
| | 3.73 ± 0.19 | 3.81 ± 0.25 | 3.69 ± 0.26 | 3.60 ± 0.22 |
| FEMALE FETUSES | | | | |
| | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. |
| | 3.55 ± 0.18 | 3.62 ± 0.24 | 3.54 ± 0.25 | 3.39 ± 0.23 |
| ‡ DEAD OR RESORBED CONCEPTUSES/LITTER | | | | |
| | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. | MEAN±S.D. |
| | 3.4 ± 3.7 | 5.9 ± 6.9 | 5.4 ± 7.0 | 3.9 ± 5.4 |

NOTE: - Animals with all implants resorbing excluded from this table.

ARGUS RESEARCH LABORATORIES, INC.
 PROTOCOL 916020 : ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF RE-1141.02 IN RATS

TABLE (PAGE 1) : FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

| | DOSAGE GROUP | | | |
|-------------------|--------------|--------------|---------------|---------------|
| | 0 MG/KG/DAY | 20 MG/KG/DAY | 100 MG/KG/DAY | 400 MG/KG/DAY |
| LITTERS EVALUATED | 23 | 25 | 25 | 25 |
| FETUSES EVALUATED | 339 | 348 | 372 | 379 |
| LIVE | 339 | 348 | 372 | 379 |
| DEAD | 0 | 0 | 0 | 0 |

Programmed STOP



Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 916-020

SPONSOR'S STUDY NUMBER: HBE BTS 0704/02

STUDY TITLE: Oral (Gavage) Developmental Toxicity Study of RE-1141.02 in Rats

PURPOSE: The purpose of this study is to detect adverse effects of RE-1141.02 on Cri:CD@BR VAF/Plus® presumed pregnant female rats and development of the embryo and fetus consequent to exposure of the dam from implantation to closure of the hard palate. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.

TESTING FACILITY: Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044-1297
USA
Telephone: (215) 443-8710
Telefax: (215) 443-8587

STUDY DIRECTOR: Raymond G. York, Ph.D., DABT
Associate Director of Research

SPONSOR: Procter & Gamble Technical Centres Ltd.
Lovett House
Lovett Road
Staines
Middlesex TW18 3AZ, UK

STUDY MONITOR: Vivienne R. Hoyle, Ph.D.
Telephone: 011-44-1784-495125
Telefax: 011-44-1784-495043

ALTERNATE CONTACT: John A. Wisler, Ph.D., DABT
The Procter & Gamble Company
Miami Valley Laboratories
11810 East Miami River Road
Ross, Ohio 45061, USA
Telephone: (513) 627-0992
Telefax: (513) 627-1167

REGULATORY CITATIONS:

U.S. Food and Drug Administration (1994). International Conference on Harmonisation; Guideline on detection of toxicity to reproduction for medicinal products. *Federal Register*, September 22, 1994, Vol. 59, No. 183.

U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58.

Japanese Ministry of Health and Welfare (1988). *Good Laboratory Practice Standard for Safety Studies on Drugs*, Pharmaceutical Affairs Bureau, April 1, 1983, amended October 5, 1988.

European Economic Community (1989). *Council decision on 28 July 1989 on the acceptance by the European Economic Community of an OECD decision/recommendation on compliance with principles of good laboratory practice*. Official Journal of the European Communities: Legislation. 32(No. L 315; 28 October): 1-17.

REGULATORY COMPLIANCE:

This study will be conducted in compliance with the Good Laboratory Practice (GLP) regulations cited above. The following description of the Testing Facility's Quality Assurance Unit (QAU) responsibilities refers to those portions of the study conducted at the Testing Facility.

All changes or revisions of this protocol shall be documented, signed by the Study Director and the Sponsor, dated and maintained with the protocol.

The QAU will audit the protocol, the raw data and the report, and will inspect all critical phases of the study in accordance with the Standard Operating Procedures of Argus Research Laboratories, Inc.

The final report will include a statement signed by the Study Director that the report accurately reflects the raw data obtained during the performance of the study and that all applicable GLP regulations were followed in the conduct of the study. Should significant deviations from GLP regulations occur, each will be described in detail, together with how the deviation might affect the quality or integrity of the study.

The QAU at Mason Laboratories will audit the raw data and the report, and will inspect critical phases of those portions of the study conducted at that facility. A separate report audited by the QAU of Mason Laboratories will be issued for the analyses. This report will appended to the final analyses report.

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE:

See ATTACHMENT 1 to the protocol.

TEST ARTICLE AND VEHICLE:**Identification:****Test Article:**

RE-1141.02 (02 refers to the lot number for this test article).

Expiration date: 30 September 98.

Information on the identity, composition, strength and activity of the test article is on file with the Sponsor.

Vehicle:

Aqueous 0.5% carboxymethylcellulose. (Supplier and lot identification for the bulk vehicle will be documented in the raw data.)

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the vehicle that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

Safety Precautions:

Gloves, mask, appropriate eye protection and uniform/lab coat to be worn during formulation preparation and dosage. The Material Safety Data Sheet (MSDS) is attached to the protocol (see ATTACHMENT 2).

Storage:

| | |
|------------------------|---|
| Bulk Test Article: | Room temperature. |
| Bulk Vehicle: | Room temperature. |
| Prepared Vehicle: | Refrigerated. |
| Prepared Formulations: | Room temperature. Prepared formulations will be stirred continuously (magnetic stir plate with stir bar). |

All test article shipments to the Testing Facility should be addressed to the attention of Julian Gulbinski, Manager of Formulations, at the previously cited address and telephone number.

Shipments should include information concerning storage conditions and shipping cartons should be labeled appropriately. The recipient should be notified in advance of sample shipment.

FORMULATION:**Frequency of Preparation:**

Formulations (suspensions) will be prepared at the Testing Facility. Preparations will be prepared weekly.

Detailed preparation procedures are attached to this protocol (see ATTACHMENT 3).

Adjustment for Activity:

The test article is 99% active, however for the purpose of dosage calculations the test article will be considered 100% active.

Testing Facility Reserve Samples:

The Testing Facility will reserve a 500 mg sample of each lot of the bulk test substance and a 500 mg or 1 mL sample of each lot of vehicle used during the course of the study. Samples will be stored under the previously cited conditions.

ANALYSES:

Samples additional to those described below may be taken if deemed necessary during the course of the study.

Bulk Test Article Sampling:

A 1 g sample of the test article will be taken on the last day of treatment and sent (ambient conditions) to the Sponsor for analysis. This sample will be sent to:

Ms. N. Lewis
Procter & Gamble Technical Centres Ltd.
Rusham Park, Whitehall Lane
Egham
Surrey TW20 9N2, UK
Telephone: 011-44-1784-474211

The recipient will be notified in advance of sample shipment.

Analyses of Prepared Formulations:**Concentration:**

Concentration of the prepared formulations will be verified during the course of this study. Duplicate samples (2 mL each) will be taken from the first and last preparation on the day prepared. One sample of each set will be shipped for analysis; the remaining samples will be retained at the Testing Facility as backup samples. Backup samples will be stored under the previously cited conditions and discarded at the Testing Facility upon the request of the Sponsor.

Stability:

Stability data for prepared formulations bracketing the range of concentrations in this study were established during the prestudy analysis of the companion dosage-range study in rats (Argus Research Laboratories, Inc., Protocol 916-020P).

Homogeneity:

Homogeneity of the prepared formulations will be verified prior to the start of this study. Triplicate samples (2 mL each) will be taken from the top, middle and bottom of the high and low concentrations on the first day prepared.

Shipping Instructions:

Samples to be analyzed will be shipped (add shipping conditions) to:

Richard Norlin
Mason Laboratories
57 Union Street
Worcester, Massachusetts 01608
USA
Telephone: (508) 791-0931
Telefax: (508) 753-1834

The recipient will be notified in advance of sample shipment.

DISPOSITION:

Prepared formulations will be discarded at the Testing Facility following approval from Sponsor. All remaining bulk test substance will be returned to:

Ms. N. Lewis
Procter & Gamble Technical Centres Ltd.
Rusham Park, Whitehall Lane
Egham
Surrey TW20 9N2, UK
Telephone: 011-44-1784-474211

The recipient will be notified in advance of shipment.

TEST SYSTEM:**Species/Strain and Reason for Selection:**

The CrI:CD@BR VAF/Plus@ (Sprague-Dawley) rat was selected as the Test System because: 1) this strain has been demonstrated to be sensitive to developmental toxins; and 2) historical data and experience exist at the Testing Facility⁽¹⁻³⁾.

Number:

Initial population acclimated: 140 virgin female rats.
Population selected for study: 100 mated female rats (25 per dosage group).

Body Weight and Age:

Female rats will be ordered to have body weights of 200 g to 250 g each at receipt, at which time they will be expected to be at least 60 days of age. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight range will be included in the final report.

Sex:

Female rats will be given the test article. Male rats of the same source and strain will be used only as breeders and are not considered part of the Test System.

Source:

Charles River Laboratories, Inc.

The rats will be shipped in filtered cartons by air freight and/or truck from Charles River Laboratories, Inc., to the Testing Facility.

Identification:

Rats are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101). Male rats are given unique permanent identification numbers upon assignment to the Testing Facility's breeder male rat population. Female rats are assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study on the basis of day 0 of presumed gestation body weights.

ANIMAL HUSBANDRY:

All cage sizes and housing conditions are in compliance with the *Guide for the Care and Use of Laboratory Animals*⁽⁴⁾.

Housing:

The rats will be individually housed in stainless steel wire-bottomed cages except during the cohabitation period. During cohabitation, each pair of rats will be housed in the male rat's cage. No nesting materials will be supplied because the female rats will be sacrificed before parturition is expected.

Room Air, Temperature and Humidity:

The animal room is independently supplied with at least ten changes per hour of 100% fresh air that has been passed through 99.97% HEPA filters (Airo Clean® room). Room temperature will be maintained at 64°F (18°C) to 79°F (26°C) and monitored constantly. Room humidity will also be monitored constantly and maintained at 30% to 70%.

Light:

An automatically-controlled 12-hour light:12-hour dark fluorescent light cycle will be maintained. Each dark period will begin at 1900 hours EST.

Diet:

Rats will be given Certified Rodent Diet® #5002 (PMI Feeds, Inc.) available *ad libitum* from individual feeders.

Water:

Water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. All water will be from a local source and passed through a reverse osmosis membrane before use. Chlorine will be added to the processed water as a bacteriostat; processed water is expected to contain no more than

1.2 ppm chlorine at the time of analysis. Water is analyzed monthly for possible bacterial contamination and twice annually for possible chemical contamination.

Contaminants:

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the certified diet or in the drinking water at levels that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier or those mentioned in this protocol will be conducted.

RANDOMIZATION AND COHABITATION:

Upon arrival, male and female rats will be assigned to individual housing on the basis of computer-generated random units. After acclimation, virgin female rats will be cohabited with breeder male rats, one male rat per female rat. The cohabitation period will consist of a maximum of five days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ* will be considered to be at day 0 of presumed gestation and assigned to individual housing.

Healthy mated female rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

ADMINISTRATION:

Route and Reason for Choice:

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it allows the systemic toxic potential of the test substance to be fully characterized.

Method and Frequency:

Female rats will be given the test article once daily on days 7 through 17 of presumed gestation, the period of organogenesis. Dosages will be adjusted daily for body weight changes and given at approximately the same time each day. Formulations will be stirred continuously (magnetic stir plate with stir bar) during dosage administration.

Rationale for Dosage Selection:

Dosages were selected on the basis of a dosage-range study (Argus Research Laboratories, Inc., Protocol 916-020P).

Dosage Levels, Concentrations and Volumes:

| Group | Number of Rats | Dosage (mg/kg/day) | Concentration (mg/mL) | Dosage Volume (mL/kg) | Argus Batch Number |
|-------|----------------|--------------------|-----------------------|-----------------------|-----------------------------|
| I | 25 | 0 (Vehicle) | 0 | 10 | B-916-020-A(Day.Month.Year) |
| II | 25 | 20 | 2 | 10 | B-916-020-B(Day.Month.Year) |
| III | 25 | 100 | 10 | 10 | B-916-020-C(Day.Month.Year) |
| IV | 25 | 400 | 40 | 10 | B-916-020-D(Day.Month.Year) |

The test article is 99% active, however for the purpose of dosage calculations the test article will be considered 100% active.

TESTS, ANALYSES AND MEASUREMENTS:**Viability:**

All Periods: At least twice daily.

Clinical Observations and/or General Appearance:

Acclimation Period: Weekly.

Predosage Period: Day 0 of presumed gestation.

Dosage Period: Daily before dosage. Postdosage observations will be recorded approximately 30 ± 10 minutes after administration.

Postdosage Period: Once daily.

Clinical observations may be recorded more frequently than cited above, if deemed appropriate by the Study Director and/or Study Monitor.

Body Weights:

Acclimation Period: Weekly.

Predosage Period: Day 0 of presumed gestation.

Dosage Period: Daily.

Postdosage Period: Daily.

Feed Consumption Values (recorded and tabulated):

Predosage Period: Day 0 of presumed gestation.
Dosage Period: Days 7, 10, 12 and 15 of presumed gestation.
Postdosage Period: Days 18 and 20 of presumed gestation.

Feed consumption values may be recorded more frequently if it is necessary to replenish the feed. These intervals will not be tabulated.

Mating Performance:

Mating will be evaluated daily during the cohabitation period and confirmed by observation of spermatozoa in a smear of the vaginal contents and/or a copulatory plug observed *in situ*.

Caesarean-Sectioning Observations:

Rats will be Caesarean-sectioned on day 20 of presumed gestation. The fetuses will be removed from the uterus and placed in individual containers. The rats will be examined for number and distribution of:

Corpora Lutea.

Implantation Sites [placentae that appear abnormal (size, color or shape) will be noted in the raw data].

Live and Dead Fetuses.

(A live fetus is defined as one that responds to stimuli; a dead fetus is defined as a term fetus that does not respond to stimuli and that is not markedly autolyzed; dead fetuses demonstrating marked to extreme autolysis are considered to be late resorptions.)

Early and Late Resorptions.

(A conceptus is defined as a late resorption if it is grossly evident that organogenesis has occurred; if this is not the case, the conceptus is defined as an early resorption.)

Fetal Observations:**Gross External Alterations and Sex:**

Fetuses will be examined for sex and for gross external alterations. Late resorptions and dead fetuses also will be examined for sex and for gross external alterations to the

extent possible but such observations will not be included in either data summarization or statistical analyses.

Body Weights and Identification:

The body weight of each fetus will be recorded. Only body weights of live fetuses will be used to determine litter fetal body weight averages. Fetuses will be tagged with identification noting study number, litter number, uterine distribution and fixative.

Soft Tissue Examination:

Approximately one-half of the fetuses in each litter will be examined for soft tissue alterations by using a variation of the microdissection technique of Staples⁽⁶⁾. The heads of these fetuses will be fixed in Bouin's solution and subsequently examined by free-hand sectioning; head sections will be stored in alcohol. The decapitated carcasses will be processed to be retained in glycerin with thymol added as a preservative.

Skeletal Examination:

The remaining fetuses (approximately one-half of the fetuses in each litter) will be examined for skeletal alterations after staining with alizarin red S⁽⁶⁾. The fetuses will be initially fixed in alcohol; skeletal preparations will be retained in glycerin with thymol added as a preservative.

Representative photographs of fetal gross, soft tissue and skeletal alterations will be taken.

METHOD OF SACRIFICE:

Rats will be sacrificed by carbon dioxide asphyxiation. Live fetuses will be sacrificed by an intraperitoneal injection of an appropriate euthanasia solution (pentobarbital sodium).

NECROPSY:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation (a table of random units will be used to select one control group rat from which all tissues examined at necropsy will be retained, in order to provide control tissues for any possible histopathological evaluations of gross lesions). All other tissues will be discarded.

Scheduled Sacrifice:

On day 20 of presumed gestation, female rats will be Caesarean-sectioned, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Uteri of

apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁷⁾.

Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition, abortion or premature delivery will be examined for the cause of death or moribund condition on the day the observation is made. The rats will be examined for gross lesions. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible, using the same methods described for fetuses. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁷⁾.

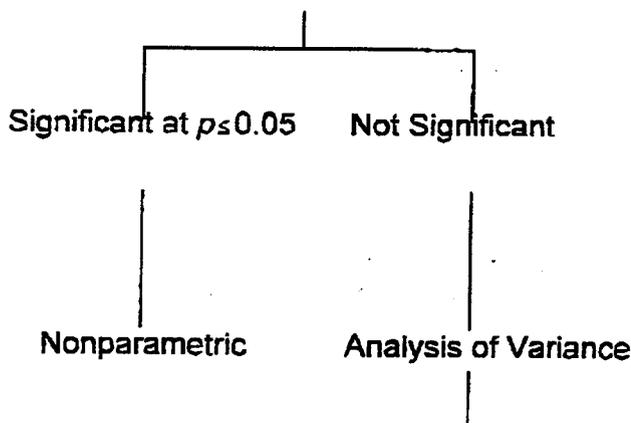
PROPOSED STATISTICAL METHODS:

Averages and percentages will be calculated. Litter values will be used where appropriate. Additional procedures and/or analyses may be performed, if appropriate.

Type of Test^a

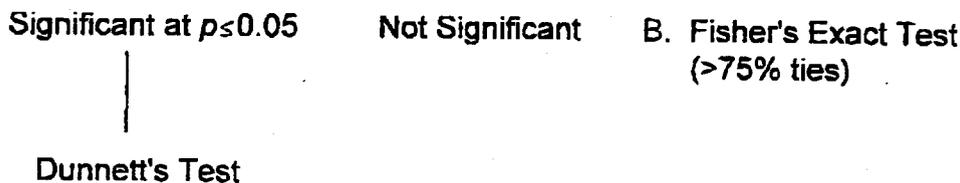
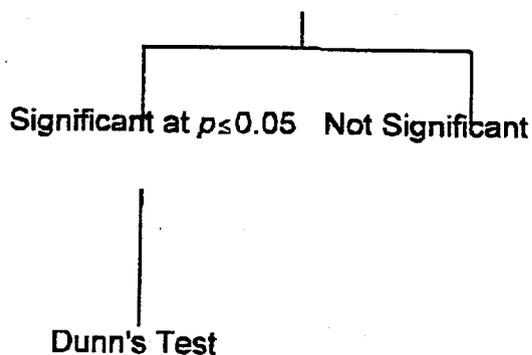
I. Parametric^b

A. Bartlett's Test^d



II. Nonparametric^c

A. Kruskal-Wallis Test
(≤75% ties)



III: Test for Proportion Data

Variance Test for Homogeneity
of the Binomial Distribution

- a. Statistically significant probabilities are reported as either $p \leq 0.05$ or $p \leq 0.01$.
- b. Used only to analyze data with homogeneity of variance.
- c. Proportion data are not included in this category.
- d. Test for homogeneity of variance.

DATA ACQUISITION, VERIFICATION AND STORAGE:

Data will be hand- and/or computer-recorded. Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records including the analytical data and report received from Mason Laboratories will be stored in the archives of the Testing Facility. All raw data, reserve samples and the final report will be stored indefinitely at the Testing Facility. All original data will be bound and indexed. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues will be stored at the Testing Facility for twenty years after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

RECORDS TO BE MAINTAINED:

All study records will be maintained including:

- Protocol and Amendments.
- Test Article, Vehicle and/or Reagent Receipt, Preparation and Use.
- Animal Acquisition.
- Randomization Schedules.
- Mating History.
- Treatment (if prescribed by Staff Veterinarian).
- General Comments.
- Clinical Observations and/or General Appearance.
- Body Weights.
- Feed Consumption Values.
- Caesarean-Sectioning and Fetal Observations.
- Gross Necropsy Observations.
- Organ Weights (if required).
- Photographs (if required).
- Study Maintenance (room and environmental records).
- Feed and Water Analyses.
- Packing and/or Shipment Lists.

KEY PERSONNEL:

- Executive Director of Research: Mildred S. Christian, Ph.D., ATS
- President and Director of Research: Alan M. Hoberman, Ph.D., DABT
- Associate Director of Research and Study Director: Raymond G. York, Ph.D., DABT
- Director of Laboratory Operations: John F. Barnett, B.S.
- Manager of Study Coordination: Valerie A. Sharper, M.S.
- Manager of Animal Operations and Chairperson, Institutional Animal Care and Use Committee: Dena C. Lebo, V.M.D.
- Manager of Regulatory Compliance: Kathleen A. Moran, M.S.
- Consultant, Veterinary Pathology: W. Ray Brown, D.V.M., Ph.D.

FINAL REPORT:

A comprehensive audited draft final report will be prepared on completion of the study and will be finalized following consultation with the Sponsor. The report will include the following:

Summary and Conclusion.

Experimental Design and Method.

Evaluation of Test Results.

Appendices: Figures, Summary and Individual Tables Summarizing the Above Data, Protocol and Associated Amendments and Deviations, Pilot Report, Study Director's GLP Compliance Statement, Analytical Report, Reports of Supporting Data (if appropriate) and Quality Assurance Unit Statement.

The Sponsor will receive four copies of the draft final report and final report. One copy of the final report should be submitted electronically on a diskette formatted for MS DOS compatibility. Copies of the reports are to be sent to:

Ms. Hilda Hessler
The Procter & Gamble Company
Maimi Valley Laboratory
11810 East Miami River Road
Ross, Ohio 45061
USA

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE STATEMENT:

The procedures described in this protocol have been reviewed by the Testing Facility's Animal Care Committee. All procedures described in this protocol that involve study animals will be conducted in a manner to avoid or minimize discomfort, distress or pain to the animals.

Unless otherwise addressed in this protocol, the Testing Facility will not use any paralytics in the course of this study. Sponsor has data on file that paralytic activity is not associated or has not been previously observed with this test article.

If necessary, animals will be relieved of pain or distress by the use of appropriate sedatives, analgesics or anesthetics unless the withholding of such agent(s) is justified for scientific reasons; the withholding of such agent(s) will continue only for the necessary period of time. Use of such agent(s), if required, will be documented in the raw data.

Animals that would otherwise experience severe or chronic pain or distress that cannot be relieved will be painlessly euthanized at the end of the procedure (or, if appropriate, during the procedure) after consultation with the Study Director and/or staff veterinarian. Methods and agents used for euthanasia will be in accordance with acceptable

standards, unless a deviation is justified for scientific reasons. The disposition of all animals purchased for this study will be documented in the raw data.

REFERENCES:

1. Christian, M.S. and Voytek, P.E. (1982). *In Vivo Reproductive and Mutagenicity Tests*. Environmental Protection Agency, Washington, D.C. National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161.
2. Christian, M.S. (1984). Reproductive toxicity and teratology evaluations of naltrexone (Proceedings of Naltrexone Symposium, New York Academy of Sciences, November 7, 1983), *J. Clin. Psychiat.* 45(9):7-10.
3. Lang, P.L. (1988). *Embryo and Fetal Developmental Toxicity (Teratology) Control Data in the Charles River Cr:CD@BR Rat*. Charles River Laboratories, Inc., Wilmington, MA 01887-0630. (Data base provided by Argus Research Laboratories, Inc.)
4. Institute of Laboratory Animal Resources (1996). *Guide for the Care and Use of Laboratory Animals*. National Academy Press, Washington, D.C.
5. Staples, R.E. (1974). Detection of visceral alterations in mammalian fetuses. *Teratology* 9(3):A37-38.
6. Staples, R.E. and Schnell, V.L. (1964). Refinement in rapid clearing technique in the KOH-alizarin red S method for fetal bone. *Stain Technol.* 39:61-63.
7. Salewski, E. (1964). Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. *Arch. Pathol. Exp. Pharmacol.* 247:367.
8. Snedecor, G.W. and Cochran, W.G. (1967). Variance test for homogeneity of the binomial distribution. *Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 240-241.
9. Sokal, R.R. and Rohlf, F.J. (1969). Bartlett's test of homogeneity of variances. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 370-371.
10. Snedecor, G.W. and Cochran, W.G. (1967). Analysis of Variance. *Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 258-275.
11. Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Amer. Stat. Assoc.* 50:1096-1129.

12. Sokal, R.R. and Rohlf, F.J. (1969). Kruskal-Wallis Test. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 388-389.
13. Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* 6(3):241-252.
14. Siegel, S. (1956). *Nonparametric Statistics for the Behavioral Sciences*, McGraw-Hill, New York, pp. 96-104.

PROTOCOL APPROVAL:

FOR THE TESTING FACILITY



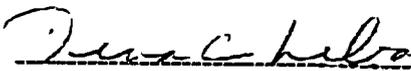
Alan M. Hoberman, Ph.D., DABT
President and Director of Research

07-JAN-98
Date



Raymond G. York, Ph.D., DABT
Associate Director of Research and
Study Director

07-JAN-98
Date



Dena C. Lebo, V.M.D.
Chairperson
Institutional Animal Care and Use Committee

07 Jan 98
Date

FOR THE SPONSOR

Information concerning the necessity for conducting this study and the fact that this is not an unnecessarily duplicative study may be obtained from the Sponsor. No alternative (*in vitro*) procedures were available for meeting the stated purposes of the study. Alternative methods to those employed in this study, which may cause more than slight or momentary pain or distress, have been considered but were not available or appropriate for this study.



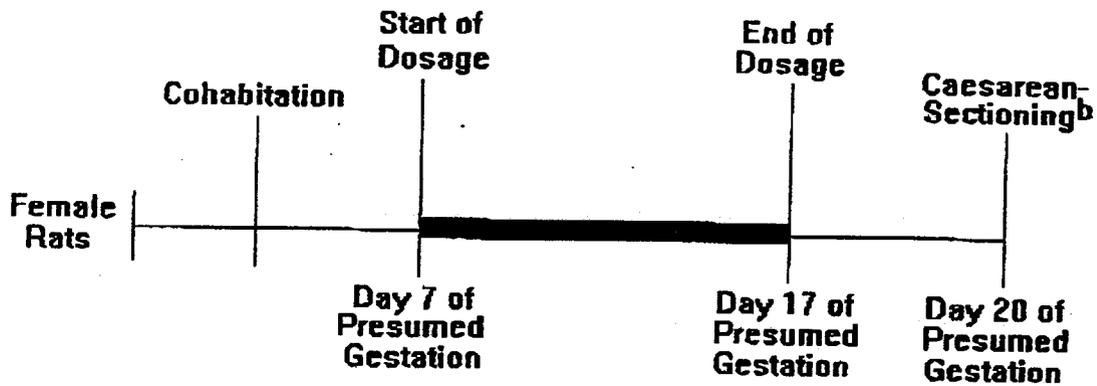
Vivienne R. Hoyle, Ph.D.
Study Monitor

12 Jan 98
Date

ATTACHMENT 1

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

STUDY SCHEMATIC
DEVELOPMENTAL TOXICITY STUDY ^a



█ = Dosage Period

a = For additional details see "Tests, Analyses and Measurements" section of the protocol

b = Fetal evaluations (all - external, 1/2 per litter - soft tissue or skeletal)

SCHEDULE^a

| | |
|-----------------------------|---|
| 13 JAN 98 | Arrival Date - Acclimation Begins. |
| 19 JAN 98 PM - 24 JAN 98 AM | Cohabitation Period. |
| 20 JAN 98 - 24 JAN 98 | Day 0 of Presumed Gestation. |
| 27 JAN 98 - 10 FEB 98 | Dosage Period (Days 7 through 17 of presumed gestation). |
| 09 FEB 98 - 13 FEB 98 | Caesarean-Sectioning Period (Day 20 of presumed gestation). |
| 12 MAY 98 | Draft Final Report. |

a. The study initiation date is the date the Study Director signs the protocol.

ATTACHMENT 2
MATERIAL SAFETY DATA SHEET

Supplier's name is confidential information
 This substance is being tested for:
 Procter and Gamble Technical centres Ltd
 Rusham Park
 Whitehall Lane
 Egham
 Surrey
 TW20 9NW
 United Kingdom

Contact name/Tel Viv Hoyle 44 1783 400125

The product name is confidential.
 Test substance identification number: RE1141.02
 Divisional Request Document Number: 0704/02 (HBE STS)

SECTION II - HAZARDOUS COMPONENTS

| HAZARDOUS COMPONENTS | % | ACGIH TLV | OSHA PEL | CAS No. |
|----------------------|---|-----------|----------|---------|
|----------------------|---|-----------|----------|---------|

SECTION III - PHYSICAL & CHEMICAL CHARACTERISTICS

BOILING Point:..... 288°C
 MELTING POINT:..... 94°C
 SPECIFIC GRAVITY (Water=1):... 1.224 @ 4°C
 VAPOR PRESSURE:..... <1mm Hg
 VAPOR DENSITY (Air=1):..... 5
 SOLUBILITY IN WATER:..... 0.03%
 REACTIVITY IN WATER:..... NOT REACTIVE
 APPEARANCE AND ODOR:..... Beige prisms or powder with a typical phenolic odor.

N/A=Not Applicable N/D=Not Determined

The product name is confidential.

Test substance identification number: RE1141.02

Divisional Request Document Number: 0704.02 (MGE 6TS)

SECTION IV - FIRE & EXPLOSION DATA

FLASH POINT (Method Used): 131°C 268°F METHOD: TCC

FLAMMABLE LIMITS

| VOLUME | LEL | UEL |
|--------|-----|-----|
| | N/D | N/D |

AUTO-IGNITION TEMPERATURE:..... >1000°C >1900°F

EXTINGUISH MEDIA:..... Water spray, Carbon dioxide, dry chemical powder, alcohol or polymer foam.

SPECIAL FIRE FIGHTING PROCEDURES:... The use of a self-contained breathing apparatus is required when fighting fires involving this material.

UNUSUAL FIRE AND EXPLOSION HAZARDS: NONE

SECTION V - PHYSICAL HAZARDS (Reactivity Data)

STABILITY:..... STABLE

CONDITIONS TO AVOID:..... NONE REPORTED

INCOMPATIBILITY

(Materials to Avoid):..... OXIDIZERS/STRONG MINERAL ACIDS/EPOXIDES

HAZARDOUS DECOMPOSITION PRODUCTS: NONE

HAZARDOUS POLYMERIZATION:..... WILL NOT OCCUR

CONDITIONS TO AVOID:..... NONE REPORTED

SECTION VI - HEALTH HAZARDS

ACUTE:

Primary routes: Oral/Dermal

Large intestines-Nephritis, vomiting, diarrhea, circulatory collapse, anemia, convulsions and death. Dermal-Kidney effects, corneal damage. Imitating to skin and eyes.

CHRONIC:

Hepatomegaly, splenomegaly, jaundice, hemolytic anemia albuminuria, hematuria.

SIGNS & SYMPTOMS OF EXPOSURE:

Conjunctivitis, corneal burns, dermatitis with hyperpigmentation, nausea, vomiting, abdominal pain headache and convulsions.

MEDICAL CONDITIONS GENERALLY AGGRAVATED BY EXPOSURE:

Blood, liver and kidney diseases.

N/A=Not Applicable N/D=Not Determined

Test substance identification number: RE1141.02
Divisional Request Document Number: 0704/02 (H&E STS)

CARCINOGENICITY NTP: NO
 IARC: NO
 OSHA: NO

EMERGENCY & FIRST AID PROCEDURES:

EYES: In case of contact with eyes, rinse immediately for at least 15 minutes and seek medical attention.
SKIN: In case of contact with skin, rinse immediately and wash with soap and water for at least 15 minutes.
INHALATION: In case of inhalation, remove to fresh air, administer oxygen if breathing is difficult. If breathing has stopped, apply artificial respiration. Seek immediate medical attention.
INGESTION: In case of ingestion seek immediate medical attention.

SECTION VII - SPECIAL PRECAUTIONS & SPILL/LEAK PROCEDURES**PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE:**

Keep in a cool place. Keep away from living quarters. Keep container tightly closed. Keep container in a well ventilated area. Keep away from food, drink and animal feedstock. Do not eat, drink or smoke when handling material. Do not breathe vapor, fumes, spray. Avoid contact with skin. Avoid contact with eyes. Wear appropriate safety equipment.

OTHER PRECAUTIONS:

Do not allow material to enter waterways, possible aquatic toxin.

STEPS TO BE TAKEN IN CASE OF RELEASE OR SPILL:

R/Q-N/A

Wear respirator, chemical safety goggles, rubber boots and heavy rubber gloves. Evacuate area. Ventilate area and wash spill site after pick-up is complete. Carefully sweep up and remove. Place in an appropriate container. Wash spill site with soap solution. Flush spill area with copious amounts of water.

WASTE DISPOSAL:

This combustible material may be burned in a chemical incinerator equipped with an afterburner and scrubber.

RCRA HAZARDOUS WASTE:

NO RCRA # N/A
CERCLA NO RG-N/A

N/A=Not Applicable N/D=Not Determined

The product name is confidential.
Test substance identification number: RE1141.02
Divisional Request Document Number: 0704/02 (LBE ETS)

SECTION VIII - PERSONAL PROTECTION/CONTROL

RESPIRATORY PROTECTION: USBM organic canister

VENTILATION: LOCAL: YES
GENERAL: YES
SPECIAL: NONE

PROTECTIVE GLOVES: RUBBER

EYE PROTECTION: CHEMICAL GOGGLES

OTHER PROTECTIVE EQUIPMENT OR CLOTHING: APRON/BOOTS

WORK/HYGENIC REQUIREMENTS: Do not eat, drink or smoke when handling material.
Wear appropriate safety equipment. Wash or dry clean contaminated clothing before re-use.

SHIPPING INFORMATION:

DOT REGULATED: YES R/G-N/A UN/NA#

SHIPPING NAME: POISONOUS SOLIDS, N.O.S.

HAZARD CLASS: 6.1-III

DOT LABEL REQUIRED: KEEP AWAY FROM FOOD

REGULATORY REQUIREMENTS: Section 313 Reporting NO

| | | |
|-------------------|-----------------|---------------|
| Contains at Least | % of CAS Number | Chemical Name |
| N/A | N/A | N/A |

SARA Hazard Class

ACUTE YES CHRONIC YES FIRE HAZARD NO
PRESSURE NO REACTIVITY NO

Although the information and recommendations set forth herein (hereinafter "Information") are presented in good faith and believed to be as correct as of the date hereof, [redacted] makes no representations as to the completeness or accuracy thereof. Information is supplied upon the condition that receiving same will make their own determination as to its suitability for their purposes prior to use. In no event will [redacted] be responsible for damages of any nature whatsoever resulting from the use of or the reliance upon information. NO REPRESENTATION OR WARRANTIES, EITHER EXPRESSED OR IMPLIED, OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR OF ANY OTHER NATURE ARE MADE HEREUNDER WITH RESPECT TO INFORMATION OR THE PRODUCT TO WHICH INFORMATION REFERS.

N/A=Not Applicable N/D=Not Determined

ATTACHMENT 3
TEST ARTICLE PREPARATION PROCEDURE

ATTACHMENT 3

Protocol 916-020

Version: 916-020 (11.NOV.97)

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TEST ARTICLE PREPARATION PROCEDURES

Test Article: RE-1141.02

Vehicle: 0.5% carboxymethylcellulose

A. Purpose:

The purpose of this procedure is to provide a method for the preparation of dosage suspensions of RE-1141.02 for oral administration to rats on Argus Study 916-020.

B. General Information:

1. All suspension containers will be labeled and color-coded. Each label will specify the protocol number, test article identification, Argus batch number, concentration, dosage level, preparation date, expiration date and storage conditions.
2. Suspensions will be prepared:
 Daily Weekly For days of use
 At least once weekly By Sponsor
3. Suspensions will be prepared at a final dosage volume of 10 mL/kg.
4. Safety:
 Gloves, lab coat, goggles or safety glasses and face shield
 Dust-Mist Respirator
 Half-Face Respirator
 Full-Face Respirator/Positive Pressure Hood
 Tyvek Suit/Apron
5. Dosage suspensions adjusted for % Activity/Purity or Correction Factor:
 Yes No (Calculations based on 100%)
 % Activity % Purity Correction Factor
6. Sampling requirements: Cited in protocol
7. Storage: Cited in protocol

ATTACHMENT 3

Protocol 916-020
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TEST ARTICLE PREPARATION PROCEDURES

C. Dosage Suspension Preparation:

1. Into an appropriately sized mortar, add the required amount of TA to prepare the appropriate dosage level (see PREPARATION CALCULATIONS).
2. Grind the test article into a fine powder, without any vehicle.
3. Slowly add small amounts of vehicle to form a thick paste. Slowly add more vehicle to form a uniform fluid suspension.
4. Once the test article has been uniformly suspended into the vehicle transfer to a pre-calibrated beaker. Rinse the mortar and pestle completely with vehicle and add to the pre-calibrated beaker.
5. Q.S. to the final desired volume with vehicle. Add a magnetic stir bar to the vessel, place on a magnetic stir plate and agitate until uniform prior to and during dosage administration and/or sampling. (Care must be taken to mix properly but not incorporate bubbles)
6. Record the time the suspension begins stirring on the magnetic stir plate and the time it is taken for dosage administration.
7. Repeat steps (1) through (6) for each concentration.

Written By: Curtis Gubinski

Approved by: [Signature] Date: 07-JAN-98

Clarification: No Yes [see attached clarification form]

Initials/Date
Written By: [Signature] 2/23/98
[Signature] 2/23/98